DOES INJECTION OF NON-DEPOLARIZING NEUROMUSCULAR BLOCKERS BEFORE THIOPENTONE AFFECT THEIR SPEED OF ONSET?

A Study of Tubocurarine and Vecuronium

I. D. LEVACK AND A. A. SPENCE

Gray and Halton (1946) in their original description of the use of tubocurarine in anaesthesia used a mixture of tubocurarine 15 mg and sodium thiopentone 500 mg as a single injection. However, Bourne (1947) recommended that tubocurarine should be injected after thiopentone from a separate syringe, because of chemical incompatibility between the two solutions, and that a different vein be used. When it became evident that the onset time of tubocurarine was a few minutes, a “reversed” sequence of tubocurarine 30 mg followed immediately by injection of up to 500 mg of sodium thiopentone using the same needle became established practice for some anaesthetists, according to Lee and Atkinson (1973). It is not known whether the order of administration affects the pharmacodynamic profile of the neuromuscular blocker.

The aim of this study was to compare the onset times of neuromuscular blockade by drugs given either before or after the induction of anaesthesia with thiopentone. Tubocurarine was studied because it was the drug for which the reversed sequence was originally described, although no measurements can be found in the literature. We also studied vecuronium as an example of a drug with a relatively faster onset of action.

PATIENTS AND METHODS

Forty healthy adult patients, younger than 60 years of age, undergoing general surgery and premedicated with papaveretum 10 mg and hyoscine 0.2 mg were studied. None had any condition in which neuromuscular blockers are contraindicated. Informed verbal consent was obtained from each patient and the study was approved by the local ethics committee.

Before the induction of anaesthesia, the patient’s left arm was abducted and the thumb connected to a force displacement transducer (Myograph 2000) in order to measure isometric twitch tension. A Myotest nerve stimulator delivered 0.2-ms impulses in a train-of-four (TOF) pattern (Roberts and Wilson, 1968) at 2 Hz repeated at 10-s intervals (Ali, Utting and Gray, 1970) and, after setting a pre-load of 30 g, a control recording was made in the conscious patient before the induction of anaesthesia. Discomfort arising from the nerve stimulation was minimized by giving the patient 50% nitrous oxide in oxygen delivered from a Magill breathing system. Arterial pressure in the arm was recorded and a venous cannula was inserted to a vein in the right forearm.

Drug doses were sodium thiopentone 4 mg kg⁻¹,
vecuronium 0.1 mg kg\(^{-1}\) and tubocurarine 0.5 mg kg\(^{-1}\); the sequences and speeds of injection are shown in table I. Each injection was given over a period of 5 s, with an intervening period of 30 s. Ventilation of the lungs was assisted as appropriate by manual inflation with 70% nitrous oxide in oxygen until there was 90% depression of the control twitch height in T1. Arterial pressure was measured before tracheal intubation; the lungs were ventilated artificially with 0.5% halothane in 70% nitrous oxide and oxygen using a conventional automatic ventilator.

The onset time of blockade was measured from the time of injection of the neuromuscular blocker, regardless of the sequence with thiopentone. The indices sought were 50% and 90% depression of control T1, and T4/T1 at 30%, 50% and 70% depression of control height in T1.

All patients were visited on the day after operation and specific enquiry was made as to any discomfort during the control recording while breathing the mixture of nitrous oxide before induction of anaesthesia.

Results are presented as mean values (± SD). Where appropriate, mean values were compared using the unpaired Student’s t test.

**RESULTS**

The four groups were broadly comparable with respect to age and body weight, although group 2 patients were on average older and heavier (table II).

**Onset of neuromuscular blockade**

The times from injection of the neuromuscular blocker to 50% and 90% depression of T1 in a TOF from control are shown in table III. In groups 1 (thiopentone–vecuronium) and 2 (vecuronium–thiopentone), 50% depression was achieved with veceuronium to within 1 s irrespective of sequence with sodium thiopentone, although the mean time to the same level of depression following tubocurarine was 9 s faster when tubocurarine was given first (group 4) (P < 0.001). Time to 90% depression by tubocurarine was twice as long as that for veceuronium. There was a difference of 13 s between groups 3 and 4 (P < 0.001) and 6 s between groups 1 and 2 (P < 0.001), but these do not suggest a systematic effect of drug sequence.

Tracheal intubation was carried out with ease at 90% depression in all patients by the same anaesthetist and no detailed assessment of intubating conditions was attempted. Systolic arterial pressure measured before tracheal intubation was greater than 95 mm Hg in every patient.

On the day after operation no patient complained that nerve stimulation (supramaximal) was painful, and it was usually described as a tapping sensation. There was no report of any muscle weakness or discomfort.

**Characteristics of neuromuscular blockade**

The relationship between T1 depression and TOF ratio following either blocker was not affected by reversing the sequence with sodium thiopentone (table IV). It was also evident that the degree of fade for a given level of T1 depression was greater with tubocurarine than with veceuronium at the doses given.
DISCUSSION

It is known that thiopentone has a direct stimulant action on muscle and prolongs the contraction time (Quilliam, 1955), but there is a simultaneous depression of neuromuscular transmission (Sirnes, 1954). A synergistic effect between sodium thiopentone and tubocurarine has been described by Dundee (1974), and Hughes (1970) showed that thiopentone potentiates the action of tubocurarine in cats, in particular the recovery time. On the other hand, cardiovascular depression after sodium thiopentone, with delay in circulation time, might be expected to slow the arrival of neuromuscular blockers at their site of action.

In spite of small, statistically significant, differences in some of the indices analysed for tubocurarine or for vecuronium, the results did not reveal either a systematic or a clinically significant difference in the pharmacodynamics of these drugs, in the doses given, when preceded or followed by thiopentone at the induction of anaesthesia.

Thus, intrinsically, there is neither advantage nor disadvantage in the reversed sequence regimen as seen with these compounds. Obviously, the prior injection of the neuromuscular blocker may help to ensure that its efficacy as regards conditions for tracheal intubation coincides with the peak anaesthetic effect of thiopentone. This presumed advantage, however, confers no obvious benefit in terms of induction–intubation interval as considered in relation to the unprotected airway. The patient is in an irretrievable process involving aspiration and ventilatory risk from the moment of the first injection, whether it be neuromuscular blocker or hypnotic.

The original intention with the reversed sequence (tubocurarine–thiopentone) was to shorten the interval between the start of induction of anaesthesia and the onset of suitable conditions for tracheal intubation. This aspect was not examined directly in the present study. Indeed, we waited deliberately until we saw 90% depression of T1 because we believed that this would yield good conditions for intubation, as was the case.

The difference in TOF ratio and T1 depression (table IV) following vecuronium or tubocurarine is probably attributable to the different pharmacodynamics and sites of action of the two drugs at the neuromuscular junction (Bowman, 1980).

REFERENCES


